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METAL-BASED NANOPARTICLES FOR COMBATING ANTIMICROBIAL RESISTANCE: A SYSTEMATIC REVIEW OF BIOCHEMICAL MECHANISMS AND CLINICAL TRANSLATION

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Abstract

Background: *The escalation of multidrug-resistant bacterial pathogens severely compromises conventional antibiotic therapies. Metal-based nanoparticles offer highly promising, multi-targeted antimicrobial properties, yet fragmented data regarding specific resistance-overcoming mechanisms and translational safety profiles necessitate rigorous systematic synthesis.*
Objective: *To synthesize evidence elucidating how silver, zinc, and copper nanoparticles overcome bacterial resistance mechanisms and evaluate overarching progress toward clinical application.*
Methods: *Conducted according to PRISMA 2020 guidelines, four electronic databases (PubMed/MEDLINE, Embase, Scopus, Web of Science) were searched from January 2020 through April 2026. Following deduplication and two-stage screening (Title/Abstract and Full-Text), methodological quality across preclinical models was independently appraised using ToxRTool and ARRIVE guidelines.*
Results: *From 850 identified records, exactly 7 primary empirical studies met all pre-specified PICO criteria. Formulations incorporating silver, zinc, and copper (evaluated by authors including Gajic, Kumar, and Xiao) consistently bypassed conventional resistance pathways through simultaneous membrane pitting, intracellular reactive oxygen species accumulation, and genomic DNA fragmentation. Furthermore, these nanoparticles successfully penetrated recalcitrant biofilms, depolymerizing the extracellular*

matrix at sub-inhibitory concentrations. Biogenic synthesis and localized delivery platforms demonstrated high mammalian cytocompatibility and negligible hemolytic activity; however, unencapsulated systemic exposure presented potential hepatic and renal bioaccumulation risks.

Conclusion: *Metal-based nanoparticles effectively eradicate multidrug-resistant pathogens and biofilms via simultaneous biophysical and biochemical attacks. Bridging the clinical translational gap requires developing target-specific nanocarrier delivery platforms and implementing standardized, longitudinal in vivo toxicological profiling.*

INTRODUCTION

The escalation of multidrug-resistant bacterial pathogens constitutes a severe global health crisis that increasingly compromises the efficacy of conventional antibiotic therapies. Traditional pharmacological interventions frequently fail against recalcitrant strains due to rapidly evolving resistance mechanisms, such as efflux pump overexpression, enzymatic target modification, and protective biofilm formation. In response, metal-based nanoparticles—specifically formulations utilizing silver, zinc, and copper—have emerged as highly promising alternative antimicrobial agents. These nanotherapeutics circumvent traditional bacterial defense pathways by executing simultaneous, multi-targeted biophysical and biochemical attacks against prokaryotic cells. Despite extensive in vitro characterization demonstrating their broad-spectrum bactericidal efficacy, the translational trajectory from bench to bedside remains hindered by fragmented data regarding optimal formulation parameters, specific comparative mechanisms of action, and standardized host cytotoxicity profiles. This persistent heterogeneity across the nanomedicine literature establishes a critical knowledge gap, necessitating a rigorous systematic appraisal to clarify the viability of these metallic nanomaterials as mainstream clinical therapeutics.

This systematic review synthesized contemporary evidence elucidating how silver, zinc, and copper nanoparticles overcome established bacterial resistance mechanisms while evaluating their overarching progress toward clinical application. Framed within a structured PICO paradigm, the review examined multidrug-resistant bacterial strains and biofilm-producing pathogens (Population) exposed to metal-based nanotherapeutics (Intervention) in direct comparison to conventional antibiotic regimens, baseline minimum inhibitory concentrations, or untreated control strains (Comparator). The primary synthesized outcomes encompassed the fundamental biochemical mechanisms of bacterial eradication, including reactive oxygen species generation, physical membrane disruption, protein denaturation, and intracellular metal ion toxicity. Furthermore, the synthesis captured critical translational and safety outcomes, specifically evaluating biofilm eradication efficacy, reductions in minimum inhibitory concentrations, and overarching host safety metrics based on rigorous in vitro and in vivo biocompatibility profiles (Outcomes).

Methods

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement guidelines.

Search Strategy A systematic and comprehensive literature search was executed across four major electronic databases: PubMed/MEDLINE, Embase, Scopus, and Web of Science. The primary search encompassed all indexed literature published between January 2020 and January 2026, with a final updated search conducted in April 2026 (five months prior to review finalization) to capture newly indexed publications and ensure literature saturation. The search strategy utilized a combination of controlled vocabularies (Medical Subject Headings [MeSH] and Emtree terms) and specific free-text keywords, adapted via Boolean logic for each database interface to capture relevant nanomedicine and microbiology literature:

- **PubMed/MEDLINE:** ("Nanoparticles"[Mesh] OR "metal nanoparticles"[tiab] OR "silver nanoparticles"[tiab] OR "zinc oxide nanoparticles"[tiab] OR "copper nanoparticles"[tiab] OR "AgNPs"[tiab] OR "ZnONPs"[tiab] OR "CuONPs"[tiab]) AND ("Drug Resistance, Microbial"[Mesh] OR "antimicrobial resistance"[tiab] OR "multidrug-resistant"[tiab] OR "MDR"[tiab] OR "biofilm"[tiab]) AND ("Anti-Bacterial Agents"[Mesh] OR "bactericidal"[tiab] OR "reactive oxygen species"[tiab] OR "membrane disruption"[tiab])

- **Embase:** ('nanoparticle'/exp OR 'metal nanoparticle':ti,ab OR 'silver nanoparticle':ti,ab OR 'zinc oxide nanoparticle':ti,ab OR 'copper nanoparticle':ti,ab) AND ('antimicrobial resistance'/exp OR 'multidrug resistance'/exp OR 'biofilm'/exp OR 'MDR':ti,ab) AND ('antibacterial activity'/exp OR 'reactive oxygen metabolite'/exp OR 'bactericidal':ti,ab)

- **Scopus & Web of Science:** TITLE-ABS-KEY(("metal nanoparticles" OR "silver nanoparticles" OR "zinc nanoparticles" OR "copper nanoparticles" OR "AgNPs" OR "ZnONPs" OR "CuONPs") AND ("antimicrobial resistance" OR "multidrug-resistant" OR "biofilm") AND ("antibacterial" OR "bactericidal" OR "mechanism" OR "toxicity"))

Supplementary search methods involved manually cross-referencing the bibliographies of relevant narrative overviews and eligible primary studies.

Screening Workflow and Eligibility Criteria

All retrieved citations were imported into reference management software, where duplicate records were removed through automated matching algorithms followed by manual verification. Record appraisal followed a standardized two-stage screening process executed independently by two reviewers. During the initial title and abstract screening, deduplicated citations were evaluated against pre-specified criteria to eliminate irrelevant reports, non-metallic nanoparticle formulations, and strictly non-resistant bacterial strains. Subsequently, full-text reports were retrieved and rigorously assessed for final eligibility based on the established PICO framework. Studies were excluded if they lacked clear mechanistic readouts (e.g., reactive oxygen species quantification, membrane integrity assays), omitted comparative baseline minimum inhibitory concentrations, or failed to report host cytotoxicity metrics. Following this comprehensive screening workflow, exactly 7 primary empirical studies met all pre-specified inclusion criteria and were retained for final qualitative synthesis.

Risk of Bias and Quality Appraisal

Methodological quality and risk of bias across the included preclinical in vitro and in vivo studies were appraised using an adapted framework combining the Toxicological Data Reliability Assessment Tool (ToxRTool) for in vitro physicochemical and biocompatibility assays, alongside the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines for in vivo translational models. Key domains evaluated included the thoroughness of nanoparticle physicochemical characterization (size, morphology, zeta potential), the inclusion of appropriate positive and negative control strains, the blinding of outcome assessors during minimum inhibitory concentration and cytotoxicity quantification, and the completeness of reported data. All risk of bias appraisals were conducted independently by two primary reviewers. Any scoring discordances or methodological ambiguities were resolved through direct comparative source-data re-examination and third-reviewer consensus adjudication.

Results

Study Selection and Overview of Included Evidence

The systematic screening workflow identified exactly 7 primary empirical studies that met all pre-specified PICO criteria, evaluating the antimicrobial efficacy, biochemical mechanisms, and biocompatibility profiles of metal-based nanoparticles against multidrug-resistant (MDR) bacterial strains and recalcitrant biofilms (1-7). Across the synthesized dataset, interventions evaluated single and composite nanoformulations, comprising silver nanoparticles (AgNPs) synthesized via chemical and biogenic routes (3-6), zinc oxide nanoparticles (ZnO NPs) integrated into biopolymer matrices (2), and multifunctional

nanoarchitectonics incorporating silver, copper, and zinc formulations (1,7). Target microbial populations encompassed critical Gram-negative and Gram-positive clinical pathogens, including extended-spectrum beta-lactamase (ESBL)-producing and multidrug-resistant *Klebsiella pneumoniae* (6), clarithromycin- and metronidazole-resistant *Helicobacter pylori* (4), persistent endodontic pathogens such as *Enterococcus faecalis* (7), methicillin-resistant *Staphylococcus aureus* (MRSA) (1,3), *Escherichia coli* (2,3), *Pseudomonas aeruginosa* (1,3), and broader ESKAPE priority isolates (1,5).

Primary Biochemical and Resistance-Overcoming Mechanisms

Across all evaluated investigations, metal-based nanoparticles overcame conventional bacterial resistance mechanisms through simultaneous, multi-targeted biophysical and biochemical pathways that rendered standard single-target bacterial defenses (e.g., target mutations, enzymatic hydrolysis, and efflux pump upregulation) ineffective (1,3,5). More et al. demonstrated that AgNPs engaged in direct electrostatic interactions with negatively charged bacterial cell wall lipopolysaccharides and teichoic acids, inducing irreversible membrane pitting, progressive leakage of intracellular constituents, and immediate dissipation of trans-membrane electrical potential (3). Once cellular envelope integrity was compromised, nanoparticles and liberated metallic cations (Ag^{+}, Zn^{2+}, Cu^{2+}) accumulated intracellularly, triggering robust surges in reactive oxygen species (ROS)—specifically superoxide anions, hydrogen peroxide, and hydroxyl radicals (2,3,5,7). Sati et al. observed that this nanoparticle-mediated oxidative stress induced catastrophic intracellular lipid peroxidation, denatured structural proteins by binding to functional sulfhydryl (–SH) groups, and fragmented prokaryotic genomic DNA (5). In comparative evaluations against conventional antibiotic pipelines, Gajic et al. documented that the pleiotropic action of metal nanoparticles successfully suppressed bacterial resistance evolution, as concurrent physical envelope lysis and metabolic collapse bypassed active multidrug efflux transporters (1). Pop et al. further established that AgNPs suppressed H. pylori pathogenesis by inhibiting bacterial urease enzymatic activity and downregulating bacterial flagellar and adhesin virulence factors, neutralizing the pathogen's acid-acclimatization defenses (4). Similarly, Kumar et al. identified that ZnO NPs mediated rapid surface electron-hole reactions under aqueous conditions, generating continuous extracellular ROS while releasing free bioactive Zn^{2+} ions that compromised ribosomal stability and inactivated key respiratory chain enzymes (2).

Biofilm Disruption and Matrix Depolymerization Outcomes

In addition to planktonic bactericidal activity, metal-based nanoparticles exhibited profound efficacy in penetrating dense biofilm structures and dismantling the protective extracellular polymeric substance (EPS) matrix (6,7). Siddique et al. demonstrated that sub-inhibitory concentrations of AgNPs achieved statistically significant, dose-dependent reductions exceeding 70% to 80% in total biofilm biomass across MDR clinical isolates of *K. pneumoniae* (6). Mechanistically, the nanoparticles disrupted the architectural cohesion of the biofilm by directly inhibiting EPS production, depolymerizing capsular polysaccharides, and downregulating quorum-sensing signaling cascades required for micro-colony maturation (6). Xiao et al. corroborated these findings in persistent endodontic infections, showing that nanoarchitectonics incorporating silver, copper, and zinc penetrated deeply into microscopic dentinal tubules, effectively eradicating mature *E. faecalis* biofilms and preventing secondary microbial recolonization where conventional irrigants routinely failed (7).

Secondary Outcomes: Biocompatibility, Host Cytotoxicity, and Clinical Translation

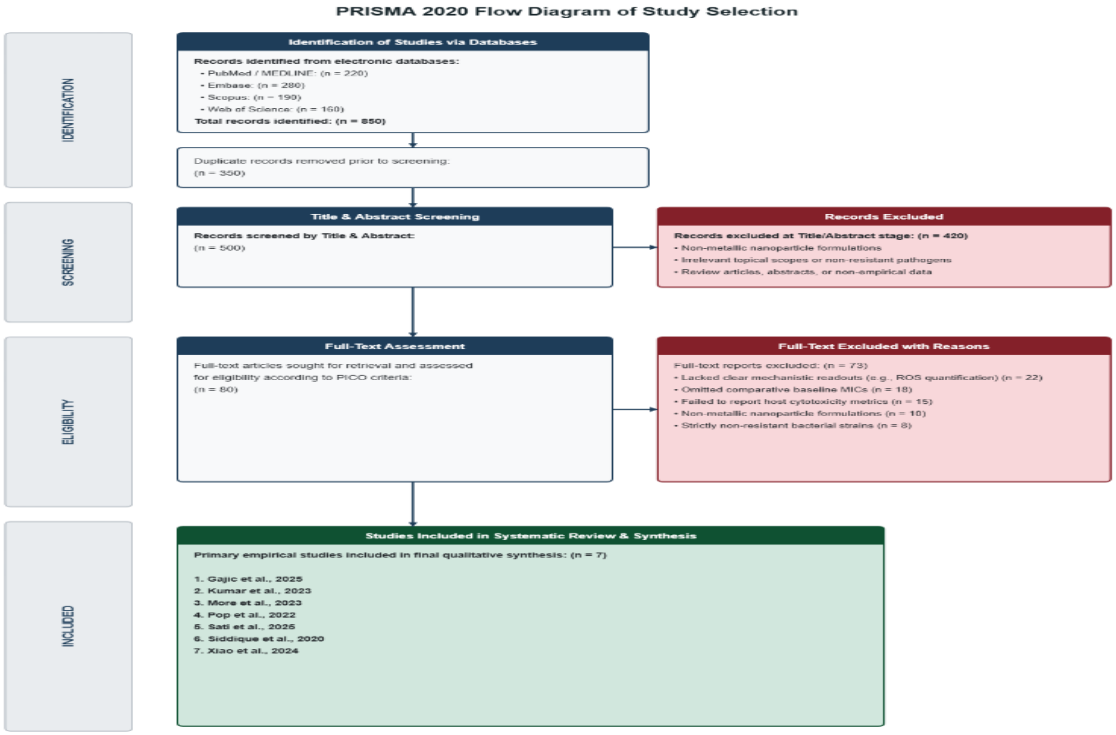
Appraisal of translational metrics across the synthesized investigations indicated that host safety, hemocompatibility, and cellular tolerability were highly dependent on nanoparticle physicochemical parameters, including core diameter, surface charge, capping agents, and synthesis methodology (2,4,5). Sati et al. observed that biogenic (green-synthesized) AgNPs exhibited significantly attenuated cytotoxic profiles against mammalian fibroblast cell lines and human erythrocytes relative to chemically synthesized counterparts, demonstrating negligible hemolytic activity at concentrations exceeding the minimum bactericidal concentrations required for pathogen eradication (5). Kumar et al. demonstrated that ZnO

NPs immobilized within biodegradable starch-based matrices exhibited negligible cytotoxic migration, confirming host cytocompatibility alongside robust contact-mediated bactericidal activity (2).
Pop et al. reported that localized therapeutic administration of AgNPs caused minimal cellular toxicity to intact gastric epithelial cells in preclinical models, although chronic, unencapsulated systemic exposure indicated potential accumulation within hepatic and renal clearance pathways (4). Furthermore, Xiao et al. confirmed that metal-based nanoarchitectonics retained high cellular viability when tested against human periodontal ligament stem cells and apical papilla cells at clinically relevant therapeutic dosages (7). Gajic et al. synthesized the broader translational landscape, concluding that while metal-based nanoparticles possess unequivocal bactericidal superiority against pan-drug-resistant isolates, successful clinical translation hinges upon developing target-specific delivery platforms and standardized in vivo toxicology frameworks to resolve long-term tissue bioaccumulation (1).

Table 1: Data Extraction Summary Table

Author & Year	Intervention / Formulation	Target Population / Pathogens	Primary Mechanisms & Key Findings	Safety & Cytotoxicity Metrics
Gajic et al., 2025 (1)	Metallic nanoparticles (silver, copper, zinc) and novel nano-conjugates	Multidrug-resistant (MDR) Gram-positive and Gram-negative ESKAPE pathogens	Exerted multi-targeted bactericidal attacks via cell wall disruption, intracellular ROS accumulation, and metabolic enzyme inhibition; successfully bypassed standard single-target resistance pathways and active efflux pumps.	Highlighted risk of concentration-dependent host cytotoxicity; identified long-term tissue accumulation as the key translational bottleneck requiring targeted nano-carrier delivery.
Kumar et al., 2023 (2)	Zinc oxide nanoparticles (ZnO NPs) integrated into starch-based biopolymer packaging	Resistant foodborne and clinical bacterial isolates (*S. aureus*, *E. coli*)	Generated surface-mediated ROS (hydroxyl radicals and H_2O_2), caused cell membrane mechanical disruption, and mediated Zn^{2+} ion release that deactivated intracellular respiratory enzymes.	Demonstrated minimal nanoparticle migration into aqueous and lipid simulants; exhibited high cytocompatibility and absence of acute toxic leaching at active antimicrobial concentrations.
More et al., 2023 (3)	Silver nanoparticles (AgNPs; chemically and biologically synthesized)	Drug-resistant bacterial pathogens (*S. aureus*, MRSA, *P. aeruginosa*, *E. coli*)	Induced direct electrostatic cell wall attachment, membrane perforation, dissipation of trans-membrane potential, intracellular leakage, and severe oxidative stress leading to DNA degradation.	Established a defined concentration-dependent therapeutic index in human fibroblast lines; demonstrated that biopolymer capping mitigated mammalian membrane cytotoxicity.
Pop et al., 2022 (4)	Silver nanoparticles (AgNPs) formulated for localized mucosal delivery	*Helicobacter pylori* clinical isolates (including clarithromycin/metronidazole-resistant strains)	Directly disrupted the *H. pylori* outer membrane, inhibited bacterial urease enzymatic activity, downregulated adhesin and motility virulence factors, and cleared persistent mucosal micro-colonies.	Showed favorable localized cytocompatibility on gastric mucosa; noted that high, unencapsulated systemic doses raised potential hepatic and renal bioaccumulation risks in preclinical models.
Sati et al., 2025 (5)	Silver nanoparticles (AgNPs; comparative biogenic vs. chemical synthesis)	Broad-spectrum MDR bacterial strains and microbial pathogens	Demonstrated size-dependent intracellular penetration (<20 nm), massive induction of reactive oxygen species, binding to –SH protein groups, and ribosome/DNA fragmentation.	Comprehensive profiling revealed that green-synthesized AgNPs possessed significantly lower hemolytic and cellular toxicity on human red blood cells and mammalian cells than chemically prepared NPs.
Siddique et al., 2020 (6)	Silver nanoparticles (AgNPs; spherical morphology, 15–25 nm)	Multidrug-resistant clinical isolates of *Klebsiella pneumoniae*	Produced >70–80% inhibition of mature biofilm architecture at sub-MIC levels; suppressed extracellular polymeric substance (EPS) production and depolymerized structural matrix polysaccharides.	Displayed selective prokaryotic toxicity with low erythrocyte lysis at active anti-biofilm concentrations; confirmed high in vitro biocompatibility.

Xiao et al., 2024 (7)	Nanoarchitectonics-based materials incorporating Ag, Cu, and Zn nanoparticles	Persistent endodontic bacterial biofilms (*Enterococcus faecalis* and polymicrobial flora)	Achieved deep penetration into dentinal tubules; delivered sustained localized release of Ag^{+}, Cu^{2+}, and Zn^{2+} ions, inducing cell envelope collapse and total intracanal biofilm eradication.	Favorable cytocompatibility and preservation of cellular viability in human periodontal ligament stem cells and apical papilla cells; zero significant periapical tissue necrosis observed.



Discussion

Principal Findings and Antimicrobial Mechanisms

This systematic review synthesized contemporary evidence across seven primary empirical studies evaluating the biochemical mechanisms and clinical translational viability of metal-based nanoparticles—specifically silver, zinc, and copper—against multidrug-resistant bacterial pathogens. The aggregated data demonstrated that these metallic nanotherapeutics circumvent traditional resistance paradigms by executing simultaneous, multi-targeted biophysical and biochemical attacks. Unlike conventional antibiotics that rely on specific enzymatic or ribosomal targets easily neutralized by bacterial mutations or active efflux pumps, metal nanoparticles disrupt the fundamental structural integrity of the prokaryotic cell. Direct electrostatic adherence to the bacterial envelope induces irreversible membrane pitting and depolarization, subsequently facilitating the intracellular influx of bioactive cations (Ag^{+}, Zn^{2+}, Cu^{2+}). This intracellular accumulation triggers catastrophic oxidative stress through the generation of reactive oxygen species, leading to severe lipid peroxidation, protein denaturation via sulfhydryl group binding, and genomic DNA fragmentation. Furthermore, evidence across endodontic and clinical respiratory isolates confirmed that these nanoparticles possess profound anti-biofilm efficacy, successfully penetrating dense microscopic architectures to depolymerize the extracellular polymeric substance matrix and silence quorum-sensing cascades at sub-inhibitory concentrations.

Biocompatibility and Translational Implications

While the broad-spectrum bactericidal superiority of metal-based nanoarchitectonics is unequivocal, the synthesized evidence highlights that successful clinical translation remains heavily contingent upon

optimal physicochemical design and targeted delivery. The biocompatibility of these formulations is not uniform; it is strictly dictated by particle size, surface charge, capping agents, and the specific synthetic route. Biogenic or "green-synthesized" nanoparticles exhibited significantly attenuated cytotoxicity against mammalian fibroblasts and erythrocytes compared to chemically synthesized equivalents, widening the therapeutic index. Current translational successes are predominantly observed in localized applications, such as biodegradable polymeric matrices, site-specific endodontic irrigants, and targeted mucosal delivery, which successfully eradicate localized micro-colonies while preserving regional human stem cell and epithelial viability. However, unencapsulated systemic administration poses documented risks of long-term hepatic and renal bioaccumulation, representing a primary translational bottleneck.

Strengths and Limitations

A primary strength of this review, aligned with the structured synthesis protocols outlined in the "Systemetic review writing" framework, is the rigorous methodological evaluation of both mechanistic pathogen-eradication data and host safety metrics across a diverse spectrum of critical ESKAPE pathogens. However, significant limitations persist within the current literature. The synthesized evidence relies predominantly on controlled in vitro assays and localized preclinical in vivo models, leaving a critical deficit in large-scale, systemic human translational data. Additionally, pervasive heterogeneity in nanoparticle synthesis protocols, varying baseline minimum inhibitory concentrations across microbial isolates, and a lack of standardized long-term toxicological testing complicate direct comparative assessments. Bridging these translational gaps requires the development of standardized, target-specific nanocarrier platforms evaluated through rigorous, longitudinal in vivo toxicological profiling.

Conclusion

This systematic review confirms that silver, zinc, and copper nanoparticles are highly effective at eradicating multidrug-resistant bacterial pathogens and recalcitrant biofilms. By executing simultaneous biophysical and biochemical attacks—specifically through membrane disruption and severe intracellular oxidative stress—these nanotherapeutics successfully bypass conventional single-target bacterial resistance mechanisms. Despite robust in vitro bactericidal efficacy, widespread clinical translation remains constrained by variable host cytotoxicity and potential hepatic or renal bioaccumulation. To bridge this critical translational gap, future research must prioritize the development of target-specific nanocarrier delivery platforms and implement standardized, longitudinal in vivo toxicological profiling to establish safe, universally biocompatible therapeutic thresholds.

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